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Memory Dysfunction in Multiple Sclerosis Corresponds to Juxtacortical Lesion Load on Fast Fluid-Attenuated Inversion-Recovery MR Images

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BACKGROUND AND PURPOSE: **MR imaging is a sensitive diagnostic tool and paraclinical marker of disease activity and prognosis in multiple sclerosis (MS), yet the role of MR imaging of MS is controversial. The aim of this study was to describe the relationship between cognitive function and MS lesion size and position, as shown on comparative images from conventional spin-echo (CSE) and fast fluid-attenuated inversion-recovery (fast FLAIR) MR studies.**

METHODS: **CSE and fast FLAIR sequences consisted of 40 noncontiguous, 3-mm-thick axial sections matched for geometric position in 18 patients with relapsing-remitting MS. Lesions were scored for size, anatomic position, and their comparative appearance on CSE and fast FLAIR images. The neuropsychological assessment tested general psychological performance, memory, and frontal lobe executive function.**

RESULTS: **Fast FLAIR images showed significantly more small (146 versus six) and medium-sized (18 versus four) juxtacortical lesions than did CSE sequences. Small juxtacortical lesions displayed only on fast FLAIR images had a distinctive appearance, suggestive of small areas of perivascular inflammation. The number of these lesions corresponded to reduced performance on the fifth and delayed trials of the Rey Auditory Verbal Learning memory function test.**

CONCLUSION: **Fast FLAIR images show small lesions at the juxtacortical boundary that are not seen on CSE studies. The presence of such lesions correlates with impaired retention of information in memory tasks, which is characteristic of cognitive problems in patients with MS.**

MR imaging provides a sensitive diagnostic tool and paraclinical marker of disease activity and prognosis in multiple sclerosis (MS) (1, 2). The role of MR imaging in the investigation and management of MS is nonetheless controversial. MR imaging is used to confirm a suspected diagnosis of MS or to exclude other possible causes of a patient's symptoms. In these circumstances, conventional spin-echo (CSE) sequences provide adequate information, revealing established plaques of demyelination with high conspicuity. CSE sequences have also been widely used to document lesion load in clinical research and therapeutic trials (3, 4). The increased speed of modern scanners allows CSE techniques to be combined with the collection of fast spin-echo (FSE) images to allow higher in-plane spatial resolution and thinner sections, which further increase the lesion load detected.

Despite the high sensitivity of CSE and FSE sequences to MS lesions, attempts to correlate patient disability, symptom expression, and disease progression have been disappointing (5). This has led many groups to investigate other MR techniques that might detect lesions with stronger symptomatic and functional correlations (6).

De Coene et al (7) described the use of a fluid-attenuated inversion-recovery (FLAIR) MR imaging sequence to increase the sensitivity of spin-echo sequences to MS lesions. The FLAIR sequence uses an initial 180° inversion pulse followed by a normal spin-echo sequence that is performed at the null point of water. The resulting sup-

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pression of CSF signal not only improves the detection of lesions at CSF surfaces but also allows the use of far higher levels of T2 weighting, with resulting increases in contrast between lesions and normal tissue. The combination of FLAIR and FSE sequences offers improvements in scan time and resolution, allowing the routine use of high-resolution fast FLAIR imaging in diagnostic protocols (8). Rydberg et al (9) described a further modification of the FLAIR sequence designed to optimize the contrast between MS lesions and normal white matter. This optimized fast FLAIR sequence depicts lesions in the prosencephalon that are not apparent on CSE images (10, 11), but it has been shown to be inferior in detecting lesions in the brain stem and cerebellum (12, 13). This observation has cast doubt on the value of the fast FLAIR sequence, and it has been argued that brain stem lesions seen on CSE sequences are likely to be more strongly related to dysfunction in MS patients (14). In practice, the correlation between lesion load on CSE images and clinical disability as measured by Kurtzke's Expanded Disability Status Scale (EDSS) or ambulatory index (AI) remains poor (6, 15–17). One possible reason for this poor correlation is that these methods of assessment are rather blunt clinical instruments, designed to document disability that is likely to interfere with independent daily living (18). Consequently, both the EDSS and AI are disproportionately weighted toward motor disability.

Cognitive problems are characterized by subcortical dysfunction and are a recognized feature of MS, providing an additional indicator of disease severity (19). Previous workers have found associations between lesion load and cognitive deficit (20–23) and have correlated specific lesion sites with specific deficits in cognitive function (24–29).

The aim of this study was to compare cognitive dysfunction with the extent and distribution of lesion load exhibited on CSE and fast FLAIR imaging sequences. The study was conducted in a cohort of 18 patients with relapsing-remitting MS. Clinical assessment included EDSS and a comprehensive battery of tests of general psychology, memory, and frontal lobe executive function.

Methods

Subjects

Twenty patients with relapsing-remitting MS were recruited from the Cerebral Function Unit of the Central Manchester Healthcare NHS Trust. Twelve patients were women (age range, 22–47 years; median age, 39 years) and six were men (age range, 31–45 years; median age, 41 years). All had clinically definite MS as defined by the Poser committee (30). None of the patients were receiving immunomodulatory treatment, and none had had a relapse for at least 3 months. The study had approval from the central ethical committee of Central Manchester Healthcare Trust and all patients gave written informed consent.

Clinical and Neuropsychological Assessment

Clinical disability was assessed by use of the EDSS (31). The neuropsychological test battery was designed to test visual and verbal memory (immediate and delayed), executive processes, motor speed, IQ, and psychological distress. The battery consisted of 10 components: 1) the National Adult Reading Test (NART), 2) the Adult Memory and Information Processing Battery (AMIPB), 3) story recall, 4) the Rey Auditory Verbal Learning Test (RAVLT), 5) 10/36 spatial recall, 6) the Symbol Digit Test, 7) the Stroop Test, 8) FAS/Word Fluency, 9) Wisconsin Card Sorting Test, and 10) a general health questionnaire.

Clinical disability was assessed by an independent neurologist, and cognitive tests were administered by an independent clinical psychologist within 1 month after MR imaging and lesion scoring.

MR Imaging

Imaging was performed on a 1.5-T clinical MR unit using a bird cage head coil. Imaging consisted of an initial three-plane T1-weighted gradient-echo localizer image followed by 40 transverse dual CSE images (2300/20,80 [TR/TE]; field of view, 230 mm; matrix, 167 × 256; section thickness, 3.0 mm with a 0.3-mm intersection gap; scan time, 6.26 minutes) and fast FLAIR images (11000/140; TI, 2600; echo train length, 24; field of view, 230 mm; matrix, 196 × 256; section thickness, 3.0 mm with a 0.3-mm intersection gap; scan time, 5:08 minutes). Scans were obtained in a transverse plane parallel to a line joining the ventral surfaces of the genu and splenium of the corpus callosum.

Lesion Classification and Scoring

Images from the CSE and fast FLAIR studies were transferred to a Phillips Easy Vision workstation (Best, the Netherlands) for analysis. The first-echo (proton density–weighted) and second-echo (T2-weighted) components of the CSE were displayed adjacent to the corresponding fast FLAIR image. The identification and scoring of lesions were made by consensual agreement between an experienced neuroradiologist and a clinical neuroscientist. Lesion identification on CSE was done on both proton density–and T2-weighted images. Where lesions extended through more than one section, they were scored as a single lesion. Identification of the lesions and avoidance of false-positive scores were guided by recent work describing the appearance of normal brain on fast FLAIR images (32).

Each lesion was classified according to anatomic position, size, and appearance on CSE and fast FLAIR images. Lesion distribution was classified as central brain stem, peripheral brain stem, cerebellum, periventricular, discrete (lesions away from the ventricles and subcortical/cortical boundary), and juxtacortical (33, 34). Lesion size was defined as 0–5 mm (size 1, small); 5–10 mm (size 2, medium); >10 mm (size 3, large); and confluent (size 4) (35). Lesion appearance was classified as similar on CSE and fast FLAIR, seen only on CSE, seen only on fast FLAIR, larger on CSE, and larger on fast FLAIR.

Interobserver variation was assessed by repeated lesion analysis of six data sets (one third of the total data group) by an experienced neuroradiologist who was blinded to the disease type, lesion scores, and cognitive function scores. The observer used an identical scoring protocol and the same guidance to the normal appearance of the brain on fast FLAIR images (32).

Statistical Analysis

The total lesion count on CSE and fast FLAIR images was compared. The comparison was performed for each lesion size in each anatomic area. As the data was not normally distributed (Kolmogorov-Smirnov 1 sample test), the comparison was performed using the Wilcoxon matched pairs signed rank test.

TABLE 1: Summary of lesion number and size per anatomic area

Area / Display	Similar on Both				Only on CSE				Only on Fast FLAIR				Larger on CSE				Larger on Fast FLAIR			
Size	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Cerebellum	96	8	1		25	1	1		29	1	1			1			1	1		
BS peripheral	19	10			6	2				3				1			1			
BS central	129	4			15	1							4				2			
Periventricular	10	47	45	50										4	14	17		16	14	25
Cortical	111	40	4		6	4			146	18	3		3	1			5	15	5	1
Discrete	117	126	23	3	13	13			15	7	2	1	5	6	2		4	11	10	2
Total	482	235	73	53	65	21	1	0	190	29	6	1	12	13	16	17	12	43	29	28

Note.—Total scores are described for each lesion size, across anatomic areas. Size 1 indicates 0–5 mm (small); 2, 5–10 mm (medium); 3, >10 mm (large); 4, confluent. CSE indicates conventional spin echo; FLAIR, fluid-attenuated inversion recovery; BS, brain stem.

The relationship between lesion scores and results of the neuropsychology tests was assessed by means of Spearman's rank correlation coefficient. This is an appropriate test for nonparametric data and is less affected by outliers in the data set than are comparable parametric techniques. The data set was tested for outliers by applying the limit of 3 SD (36). Tests were performed on all independent classification groups derived from the scores of lesion size, anatomic region, and imaging appearances described above.

Since the NART-IQ predicts premorbid intelligence, it was treated as a confounding variable in the analysis of the remainder of the psychological test battery. Similarly, the Symbol Digit Test was counted as a confounding variable in the analysis of tests of executive frontal functions (Stroop, Fluency, and WCST). Where a significant correlation was found between a lesion score and a confounding variable, Spearman's rank partial correlation was performed on the other significant correlations in that grouping to remove the confounding effect. When both confounding variables were significant, then all variables were ranked and a second-order Pearson's partial correlation analysis was performed on the ranks to obtain the equivalent of a Spearman's partial coefficient. Owing to the number of analyses performed, the probability considered significant was decreased to $P < .01$ to reduce the frequency of type II errors. Interobserver variation was assessed by Bland and Altman analysis (37).

The Bland and Altman analysis, Wilcoxon matched pairs signed rank sum test, Spearman's rank correlation coefficient, and ranked Pearson's partial correlation were from the Statistics Package for the Social Sciences (SPSS, Chicago, IL). Spearman's partial rank correlation coefficient was modeled in Excel (Microsoft).

Results

Eighteen of the 20 patients completed the MR imaging and neuropsychological components of the study. The mean EDSS score in women was 3 (range, 1.5–4.5); in men, the mean score was 3.5 (range, 2.5–5.0).

The results of the MR study are shown in Table 1. A comparison of the total number of lesions on CSE and fast FLAIR images revealed a significant increase in small ($P < .01$) and medium-sized ($P < .02$) cortical lesions on the fast FLAIR images. This difference was reflected in comparisons of the supratentorial and whole-brain lesion loads, which also revealed significantly ($P < .01$) more lesions on the fast FLAIR images. Juxtacortical lesions were seen in all 18 patients, but lesions not seen on CSE images were identified on fast FLAIR images in 15 cases. The majority of juxtacortical lesions were at the gray/white matter interface. Most were very small and were typically seen in groups around the base of a sulcus. In many cases, the lesions were ovoid in shape, lying parallel and perpendicular to the gray/white matter interface (Fig 1).

Small cortical lesions (0–5 mm) depicted only on the fast FLAIR images correlated significantly with reduced performance in the fifth trial ($P = .007$) and in the delayed trial ($P = .005$) of the RAVLT (Table 2). Both tests assess delayed verbal memory function. Medium-sized cerebellar lesions seen on both fast FLAIR and CSE images correlated with the second trial of the RAVLT ($P < .001$).

Correlations between EDSS and lesion scores are shown in Table 3. Small lesions in the cerebellum, seen on both sequences, correlated with the cerebellar FS score ($r = .6$, $P = .008$). Small cerebellar lesions seen on CSE images also correlated with EDSS score ($r = .63$), although lesions seen on fast FLAIR images did not. Small periventricular lesions seen on CSE ($r = .7$, $P = .001$) and fast FLAIR ($r = .7$, $P = .001$) images correlated with the bladder dysfunction component of the EDSS. Confluent periventricular lesions seen on CSE ($r = .64$, $P = .004$) and fast FLAIR ($r = .64$, $P = .004$) images correlated with the brain stem disability component. Large (> 10 mm) discrete lesions depicted on CSE images correlated with the pyramidal disability component ($r = .59$, $P = .001$).

Repeated lesion analysis scored nearly 400 lesions for the comparative six-patient data sets. Analysis of agreement found any variation in lesion score to lie within 2 SD of the mean (Fig 2). The data point that can be identified in Figure 2 as having a difference of 17 and a mean of 105 is the score for small cortical lesions (0–5 mm). This reflects the fact that the second observer identified more small cortical lesions than the initial observers did (112 versus 95).

All analyses performed in the study used the lesion scores from the first scoring. Correlation analysis found no significant effect ($P > .05$) relating

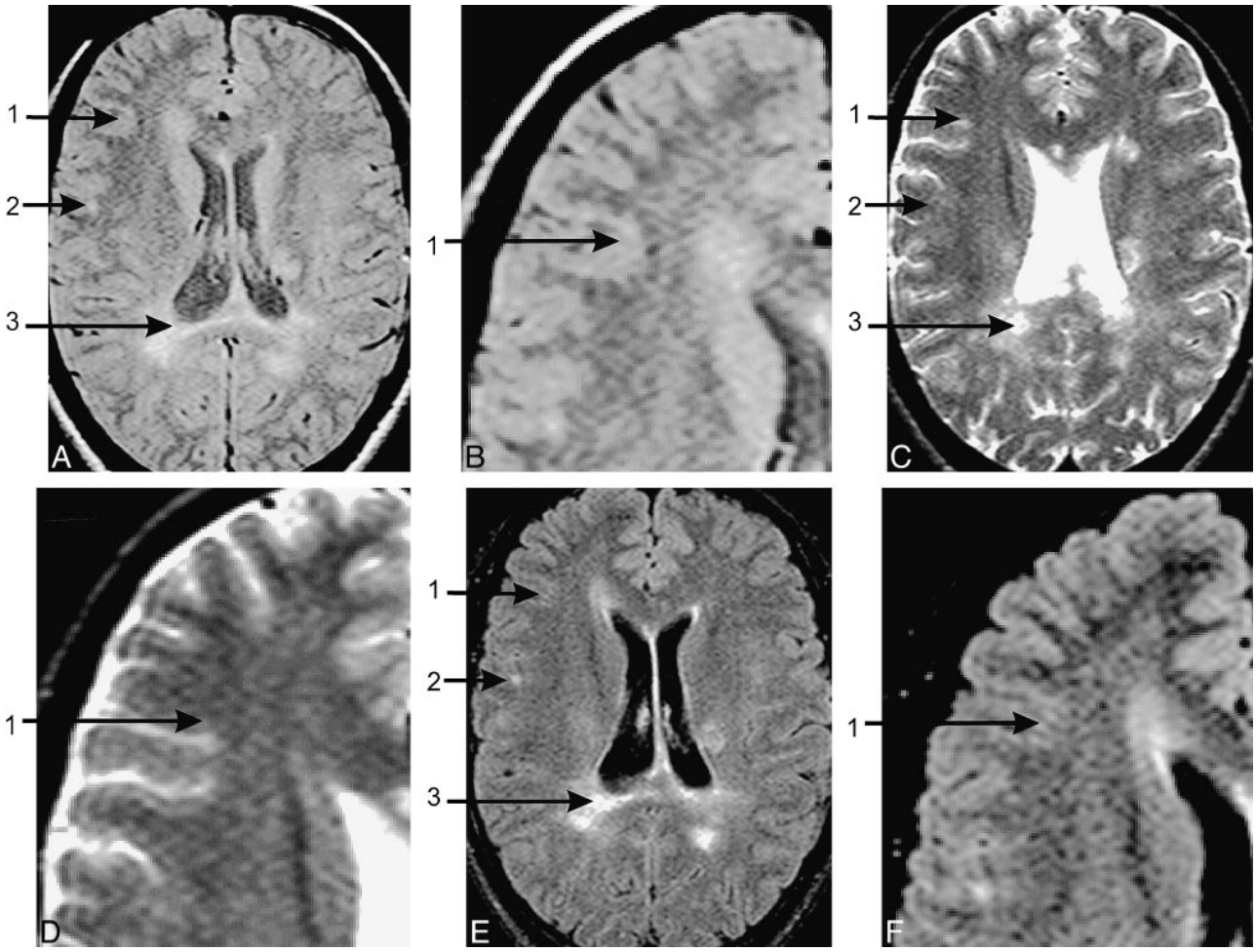

FIG 1. *A–F,* Matching lesions on proton density–weighted (*A*), T2-weighted CSE (*C*) and fast FLAIR (*E*) images. *1* denotes a population of lesions in the gray matter, extending to the juxtacortical boundary, which are evident on fast FLAIR but not on proton density— or T2-weighted CSE images. These lesions are further demonstrated on the magnified (×2) proton density–weighted (*B*) T2-weighted CSE (*D*), and fast FLAIR (*F*) images. *2* indicates a population of lesions that are less conspicuous on proton density– and T2-weighted CSE images (*C*). *3* relates to a medium-sized white matter lesion that is obvious on all imaging sequences.

TABLE 2: Lesion scores found to correlate ($P < .01$) with a cognitive function deficit

	Cognitive Test		Seen on Both		Only CSE		Only on Fast Flair	
Group	Test	Function	*r*	*P*	*r*	*P*	*r*	*P*
Medium-sized cerebellar lesions	RAVLT 2	Verbal Memory	.75	.000	.0725	.001		
Small cortical lesions	RAVLT 5	Verbal Memory					.609	.007
Small cortical lesions	RAVLT D	Verbal Memory					.63	.005

Note.—RAVLT indicates Rey Auditory Verbal Learning Test; RAVLT 2 is trial 2, RAVLT 5 is Trial 5, and RAVLT D is the delayed trial.

TABLE 3: Lesion scores found to significantly correlate ($P < .01$) with EDSS or FS score

		Seen on Both		Seen on CSE		Seen on Fast Flair	
Lesion Group	Functional Score	r_s	*P*	r_s	*P*	r_s	*P*
Small cerebellar	Cerebellar	−.6	.008				
Small periventricular	Bladder	.702	.01	.702	.001	.702	.001
Confluent periventricular	Brain stem	.641	.004	.641	.004	.641	.004
Confluent discrete	Pyramidal			−.585	.001		

Note.—Flair indicates fluid-attenuated inversion recovery; CSE, conventional spin echo; EDSS, Expanded Disability Status Scale.

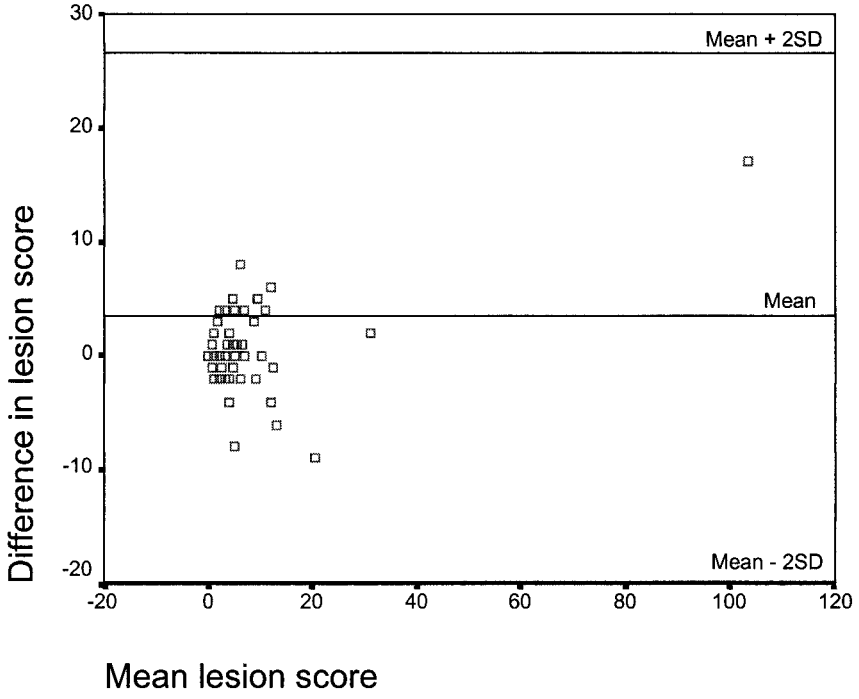

FIG 2. Bland and Altman plot shows the differences against mean for interobserver variation data.

to an increase in the size of the values. Furthermore, Wilcoxon matched pairs analysis found no significant difference ($P > .05$) between the two sets of lesion scores.

Discussion

Cognitive dysfunction is evident in up to 65% of MS patients (38) and is known to affect patients from an early stage of the disease (24). MS sufferers consider cognitive dysfunction to be more devastating than physical disability because of its dramatic effect on relationships with friends and family (39). Since the association between T2 lesion scores and clinical disability as assessed by EDSS is limited, an alternative strategy is to relate pathologic changes evident on MR images to neuropsychological function.

The fast FLAIR sequence has received considerable attention and has been widely used in the study of MS (14). It has consistently been found to be superior to CSE or FSE in depicting lesions in the prosencephalon but inferior in the posterior fossa and cervical cord (10, 11). It has the greatest sensitivity to active lesions when unenhanced images are used (38) and is the most reliable sequence for lesion quantification when semiautomated techniques are employed (40). This study confirms the findings of previous investigators that fast FLAIR images show more lesions in the prosencephalon than do CSE sequences. The increase in the number of lesions detected is largely due to the demonstration of small lesions in the cortex at the cortical/subcortical boundary. The detection of these small lesions is difficult, with an 18% increase in identification by the second observer in this study; however, it is important, as they constitute nearly 20% of the total lesion load (41).

Lesions in the cortex and at the cortical/subcortical boundary may affect the function of U fibers, which provide interconnections between cortical areas. Miki et al (29) recently investigated the effect of U fiber lesions in MS and found that patients with multiple U fiber lesions performed significantly worse on cognitive tests of memory function than did unaffected persons. These observations were based on the demonstration of small numbers of cortical or juxtacortical lesions on CSE images in 53% of patients. In the present study, no correlation was found between memory dysfunction and juxtacortical lesion load on CSE images, possibly reflecting the smaller patient sample or a methodological difference in the lesion identification technique. The appearance of these small lesions is nonetheless distinctive. They are commonly ovoid and perpendicular to the gray/white matter interface, often at the base of major sulci. These appearances agree with the common histologic finding of perivascular inflammatory infiltration around penetrating cortical vessels (42). Use of the fast FLAIR sequence increased the number of cortical and juxtacortical lesions seen by over 100%. The number of small cortical lesions depicted on fast FLAIR images correlated closely with impairment on cognitive tests of delayed memory.

Previous researchers included juxtacortical lesions in a four-parameter model that best predicts conversion to clinically definite MS at first presentation (43), suggesting that juxtacortical lesions have prognostic implications not associated with some other, more commonly quantified lesions. This is supported by the finding that verbal mem-

ory was the only cognitive function that showed continuing decline over a 4-year follow-up period (44) and that did not improve after remission in mildly impaired MS patients (45). If juxtacortical lesions do represent a correlate of progressive neurologic deficit that does not remit between attacks, it seems reasonable to hypothesize that they are associated with permanent neuronal damage. In fact, lesions that are conspicuous on T2-weighted images are known to contain transected axons (46). In the juxtacortical area, this type of axonal injury would affect the dense interconnecting cortical U fibers, causing cortical disconnection syndromes. This is supported by the finding that cerebral atrophy can be detected in MS patients and that the rate of progression of atrophy is linked to the rate of increasing disability in MS (47).

The disruption of longer cortical association fibers may also play a part in the impairment of delayed memory demonstrated in this study. The hallmark of memory impairment in subcortical disease is inefficient retrieval of information in the presence of near normal learning ability. Memory performance in this study was consistent with this model, as we found no correlation between early verbal memory tasks and lesions, but strong links with delayed memory tasks.

Although the significance of the anatomic distribution of juxtacortical lesions was not examined in the current study, evidence exists of a direct relationship between lesion sites and memory dysfunction. Lesions of the deep white matter in the left parietal lobe have been found to be associated with impaired performance on the paired associates test, a test of learning and memory (24). This suggests disruption of the arcuate longitudinal fasciculus, which sweeps through this region in a large bundle. It connects the superior and middle frontal gyri to large sections of the frontal lobe, possibly affecting the ability of the brain to encode novel verbal associations. The combined gray/white matter lesion load in the left frontal lobe has also been shown to correlate with reduced performance on memory tasks (25). Temporal lobe lesions in the corona radiata, internal capsule, insula, and hippocampus have also been linked to memory problems (27). Poor memory retrieval is characteristic of the subcortical dysfunction evident in MS. Further dysfunction is evident by assessment of problem solving and abstract conceptualization, processing of information, and an absence of aphasia, agnosia, or apraxia, except in isolated cases (24).

In addition to the correlation between juxtacortical lesion load and memory dysfunction, correlations were also found between medium-sized cerebellar lesions and immediate verbal memory tasks. Functional studies of memory have identified hypometabolism in the cerebellum of cognitively impaired MS patients (48). Although these changes may simply represent cerebellar diaschisis, the role of the cerebellum in higher cognitive functioning remains unclear (49). The number of cerebellar lesions in the present study was small, and it is possible that this observation would not be substantiated in larger studies.

Further relationships were found between individual functional system scores and lesions identified on both sequences and on the sequences in isolation. The individual functional scores are relatively high in comparison with established work in the area, and this is most probably explained by the methodological differences, such as the differing disease durations, the different number of patients, and the differences in lesion assessment between such cross-sectional studies (21). No correlation was found between the overall EDSS score and any lesion score. This highlights the variability in results of lesion/clinical disability analysis and reinforces the need for alternative methods of assessing the effect of pathologic change.

Conclusion

We have demonstrated a relationship between small juxtacortical lesions and memory dysfunction in patients with relapsing-remitting MS. These lesions are not well seen on CSE sequences and their accurate demonstration requires the use of a fast FLAIR sequence. There is growing evidence in the literature to suggest that cognitive dysfunction of this type is an important, though underused, marker of morbidity in MS. Other studies have suggested that juxtacortical lesions represent an important prognosticator of disease progression. The insights drawn in this study must be tempered by recognition of the small patient group used. Nevertheless, on the basis of our own and previous findings, we believe that the use of the fast FLAIR sequence is potentially important, as it depicts areas of pathologic processes that have been found to relate to clinical disability scores and, in particular, to neuropsychological function.

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References

1. Thompson AJ, Kermode AG, Wicks D, et al. **Major differences in the dynamics of primary and secondary progressive multiple sclerosis.** *Ann Neurol* 1991;29:53–62
2. O'Riordan JI, Thompson AJ, Kingsley DPE, et al. **The prognostic value of brain MR in clinically isolated syndromes of the CNS: a 10-year follow up.** *Brain* 1998;121:495–503
3. Paty DW, Li DKB, Duquette P, et al. **Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: 2, MR analysis results of a multicenter, randomized, double-blind, placebo-controlled trial.** *Neurology* 1993;43:662–667
4. Duquette P, Despault L, Knobler RL, et al. **Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial.** *Neurology* 1995;45:1277–1285
5. Filippi M, Horsfield MA, Tofts PS, Barkhof F, Thompson AJ, Miller DH. **Quantitative assessment of MR lesion load in monitoring the evolution of multiple sclerosis.** *Brain* 1995;118:1601–1612

6. Van Walderveen MAA, Barkhof F, Hommes OR, et al. **Correlating MR and clinical-disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR short-TE (T1-weighted) spin-echo images.** *Neurology* 1995;45:1684–1690
7. De Coene B, Hajnal JV, Gatehouse P, et al. **MR of the brain using fluid-attenuated inversion recovery (FLAIR) pulse sequences.** *AJNR Am J Neuroradiol* 1992;13:1555–1564
8. Rydberg JN, Hammond CA, Grimm RC, et al. **Initial clinical experience in MR imaging of the brain with a fast fluid-attenuated inversion-recovery pulse sequence.** *Radiology* 1994;193: 173–180
9. Rydberg JN, Riederer SJ, Rydberg CH, Jack CR. **Contrast optimization of fluid-attenuated inversion-recovery (FLAIR) imaging.** *Magn Reson Med* 1995;34:868–877
10. Boggild MD, Williams R, Haq N, Hawkins CP. **Cortical plaques visualized by fluid-attenuated inversion recovery imaging in relapsing remitting multiple sclerosis.** *Neuroradiology* 1996;38: S10–S13
11. Stevenson VL, Gawne Cain ML, Barker GJ, Thompson AJ, Miller DH. **Imaging of the spinal cord and brain in multiple sclerosis: a comparative study between fast FLAIR and fast spin echo.** *J Neurol* 1997;244:119–124
12. Filippi M, Yousry T, Baratti C, et al. **Quantitative assessment of MR lesion load in multiple sclerosis: a comparison of conventional spin-echo with fast fluid attenuated inversion recovery.** *Brain* 1996;119:1349–1355
13. Gawne Cain ML, O'Riordan JI, Thompson AJ, Moseley IF, Miller DH. **Multiple sclerosis lesion detection in the brain: a comparison of fast fluid-attenuated inversion recovery and conventional T2-weighted dual spin echo.** *Neurology* 1997;49:364–370
14. Gawne Cain ML, O'Riordan JI, Coles A, Newell B, Thompson AJ, Miller DH. **MR lesion volume measurement in multiple sclerosis and its correlation with disability: a comparison of fast fluid attenuated inversion recovery (fFLAIR) and spin echo sequences.** *J Neurol Neurosurg Psychiatry* 1998;64:197–203
15. Riahi F, Zijdenbos A, Narayanan S, et al. **Improved correlation between scores on the Expanded Disability Status Scale and cerebral lesion load in relapsing-remitting multiple sclerosis: results of the application of new imaging methods.** *Brain* 1998; 121(Pt 7):1305–1312
16. Mammi S, Filippi M, Martinelli V, et al. **Correlation between brain MR lesion volume and disability in patients with multiple sclerosis.** *Acta Neurol Scand* 1996;94:93–96
17. Filippi M, Paty DW, Kappos L, et al. **Correlations between changes in disability and T2-weighted brain MR activity in multiple sclerosis: a follow-up-study.** *Neurology* 1995;45:255–260
18. Thompson AJ, Hobart JC. **Multiple sclerosis: assessment of disability and disability scales.** *J Neurol* 1998;245:189–196
19. Hohol MJ, Guttmann CRG, Orav J, et al. **Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis.** *Arch Neurol* 1997;54:1018–1025
20. Rao SM, Leo GJ, Staubinfaubert P. **On the nature of memory disturbance in multiple sclerosis.** *J Clin Exp Neuropsychol* 1989; 11:699–712
21. Rovaris M, Filippi M, Falautano M, et al. **Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis.** *Neurology* 1998;50:1601–1608
22. Gonzalez CF, Swirsky-Sacchetti T, Mitchell D, Lublin FD, Knobler RL, Ehrlich SM. **Distributional patterns of multiple sclerosis brain lesions.** *J Neuroimaging* 1994;4:188–195
23. Patti F, Failla G, Ciancio MR, Lepiscopo MR, Reggio A. **Neuropsychological, neuroradiological and clinical findings in multiple sclerosis: a 3 year follow-up study.** *Eur J Neurol* 1998;5: 283–286
24. Ryan L, Clark CM, Klonoff H, Li D, Paty D. **Patterns of cognitive impairment in relapsing-remitting multiple sclerosis and their relationship to neuropathology on magnetic-resonance images.** *Neuropsychology* 1996;10:176–193
25. Swirsky Sacchetti T, Mitchell DR, Seward J, et al. **Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis.** *Neurology* 1992;42:1291–1295
26. Arnett PA, Rao SM, Bernardin L, Grafman J, Yetkin FZ, Lobeck L. **Relationship between frontal lobe lesions and Wisconsin card sorting test performance in patients with multiple sclerosis.** *Neurology* 1994;44:420–425
27. Tsolaki M, Drevelegas A, Karachristianou S, Kapinas K, Divanoglou D, Routsonis K. **Correlation of dementia, neuropsychological and MR findings in multiple sclerosis.** *Dementia* 1994; 5:48–52
28. Barkhof F, Elton M, Lindeboom J, et al. **Functional correlates of callosal atrophy in relapsing-remitting multiple sclerosis patients: a preliminary study.** *J Neurol* 1998;245:153–158
29. Miki Y, Grossman RI, Udupa JK, et al. **Isolated U-fiber involvement in MS: preliminary observations.** *Neurology* 1998;50: 1301–1306
30. Poser CM, Paty DW, Scheinberg L, et al. **New diagnostic criteria for multiple sclerosis: guidelines for research protocols.** *Ann Neurol* 1983;13:227–231
31. Kurtzke JF. **On the evaluation of disability in multiple sclerosis.** *Neurology* 1961;11:8:686–693
32. Gawne Cain ML, Silver NC, Moseley IF, Miller DH. **Fast FLAIR of the brain: the range of appearances in normal subjects and its application to quantification of white-matter disease.** *Neuroradiology* 1997;39:243–249
33. Ormerod IEC, Miller DH, McDonald WI, et al. **The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study.** *Brain* 1987;110: 1579–1616
34. Bastianello S, Bozzao A, Paolillo A, et al. **Fast spin-echo and fast fluid-attenuated inversion-recovery versus conventional spin-echo sequences for MR quantification of multiple sclerosis lesions.** *AJNR Am J Neuroradiol* 1997;18:699–704
35. Yousry TA, Filippi M, Becker C, Horsfield MA, Voltz R. **Comparison of MR pulse sequences in the detection of multiple sclerosis lesions.** *AJNR Am J Neuroradiol* 1997;18:959–963
36. Barlow RJ. ***Statistics: A Guide to the Use of Statistical Methods in the Physical Sciences.*** New York: Wiley; 1989:37
37. Bland MJ, Altman DG. **Statistical methods for assessing agreement between 2 methods of clinical measurement.** *Lancet* 1986; 1:307–310
38. Rao SM. **White-matter disease and dementia.** *Brain Cogn* 1996; 31:250–268
39. Rothwell PM, McDowell Z, Wong CK, Dorman PJ. **Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis.** *BMJ* 1997;314:1580–1583
40. Filippi M, Mastronardo G, Bastianello S, et al. **A longitudinal brain MR study comparing the sensitivities of the conventional and a newer approach for detecting active lesions in multiple sclerosis.** *J Neurol Sci* 1998;159:94–101
41. Filippi M, Horsfield MA, Rovaris M, et al. **Intraobserver and interobserver variability in schemes for estimating volume of brain lesions on MR images in multiple sclerosis.** *AJNR Am J Neuroradiol* 1998;19:239–244
42. Wang LQ, Lai HM, Thompson AJ, Miller DH. **Survey of the distribution of lesion size in multiple sclerosis: implication for the measurement of total lesion load.** *J Neurol Neurosurg Psychiatry* 1997;63:452–455
43. Gean-Marton AD, Vezina LG, Marton KI. **Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis.** *Radiology* 1991;180:215–221
44. Barkhof F, Filippi M, Miller DH, et al. **Comparison of MR criteria at first presentation to predict conversion to clinically definite multiple sclerosis.** *Brain* 1997;120:2059–2069
45. Sperling RA, Guttmann CR, Hohol MJ, et al. **Cognitive performance and regional lesion burden in multiple sclerosis.** *Ann Neurol* 1997;42:M3
46. Foong J, Rozewicz L, Quaghebeur G, Thompson AJ, Miller DH, Ron MA. **Neuropsychological deficits in multiple sclerosis after acute relapse.** *J Neurol Neurosurg Psychiatry* 1998;64:529–532
47. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. **Axonal transection in the lesions of multiple sclerosis.** *N Engl J Med* 1998;338:278–285
48. Losseff NA, Wang L, Lai HM, et al. **Progressive cerebral atrophy in multiple sclerosis: a serial study.** *Brain* 1996;119: 2009–2019
49. Paulesu E, Perani D, Fazio F, et al. **Functional basis of memory impairment in multiple sclerosis: a [F-18] FDG PET study.** *Neuroimaging* 1996;4:87–96
50. Thompson RF, Bao S, Chen L, et al. **Associative learning.** In: Schmahmanns JD, ed. *International Review of Neurobiology: The Cerebellum and Cognition.* London: Academic Press; 1997; 41: 152–191